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| PAGES TO FOLLOW COVER | 9 | USER ID | 6871 | CMID NUMBER | 030227.0027 | | | | | | | | |
| TO <table border="1"> <thead> <tr> <th>RECIPIENT</th> <th>COMPANY</th> <th>TELEPHONE</th> <th>FAX</th> </tr> </thead> <tbody> <tr> <td>TC1600-Customer Service (Group Art Unit 1619)</td> <td>USPTO</td> <td>(800) 786-9199</td> <td>(703) 872-9305</td> </tr> </tbody> </table> | | | | | | RECIPIENT | COMPANY | TELEPHONE | FAX | TC1600-Customer Service (Group Art Unit 1619) | USPTO | (800) 786-9199 | (703) 872-9305 |
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| FROM <table border="1"> <thead> <tr> <th>SENDER</th> <th>EMAIL</th> <th>TELEPHONE</th> <th>FAX</th> </tr> </thead> <tbody> <tr> <td>Diana L. Bush, Ph.D.</td> <td>DBush@Brobeck.com</td> <td>(858) 720-2885</td> <td>(858) 720-2555</td> </tr> </tbody> </table> | | | | | | SENDER | EMAIL | TELEPHONE | FAX | Diana L. Bush, Ph.D. | DBush@Brobeck.com | (858) 720-2885 | (858) 720-2555 |
| SENDER | EMAIL | TELEPHONE | FAX | | | | | | | | | | |
| Diana L. Bush, Ph.D. | DBush@Brobeck.com | (858) 720-2885 | (858) 720-2555 | | | | | | | | | | |
| MESSAGE Re: U.S. Patent Application Serial No. 09/978,454 Group Art Unit 1619 Filing Date: October 15, 2001 Please find the attached Third Preliminary Amendment in the above-referenced matter. | | | | | | | | | | | | | |
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March 27, 2002

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| Diana L. Bush, Ph.D. | DBush@Brobeck.com | (858) 720-2885 | (858) 720-2555 |

MESSAGE

Re: U.S. Patent Application Serial No. 09/978,454
Group Art Unit 1619
Filing Date: October 15, 2001

Please find the attached Third Preliminary Amendment in the above-referenced matter.

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FROM

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Diana L. Bush, Ph.D.

DBush@Brobeck.com

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MESSAGE

Re: U.S. Patent Application Serial No. 09/978,454
Group Art Unit 1619
Filing Date: October 15, 2001

Please find the attached Third Preliminary Amendment in the above-referenced matter.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Erion *et al.*

Serial No.: 09/978,454

Filed: October 15, 2001

Title: NOVEL PRODRUGS FOR
PHOSPHORUS-CONTAINING
COMPOUNDS

Group Art Unit: 1619

Examiner: To Be Assigned

Commissioner for Patents
Washington, D.C. 20231

THIRD PRELIMINARY AMENDMENT

Dear Sir:

Prior to examination of the subject application, Applicants request that the Examiner enter the following amendments. It is believed that no additional fee is due for filing this amendment. If, however, any fee should become due or credit become payable during the pendency of these proceedings, the Examiner is authorized to charge or credit the same to deposit account number 50-1273.

AMENDMENTS

In the Claims

Please add new claims as follows:

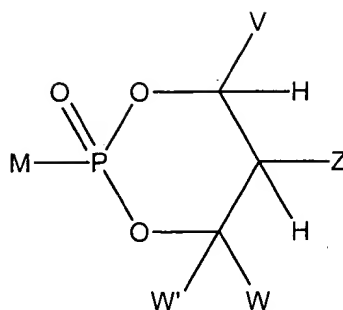
--14. (New) A pharmaceutical composition comprising a compound of Formula I:

CERTIFICATE OF TRANSMISSION
(37 C.F.R. §1.8)

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Formula I

wherein:

V, W and W' are independently selected from the group consisting of hydrogen, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, wherein the cyclic group optionally contains one heteroatom and is substituted with a hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxy carbonyloxy group attached to a carbon atom that is three atoms away from both oxygen atoms that are attached to the phosphorus atom; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group wherein the cyclic group optionally contains one heteroatom, and is fused to an aryl group, at the beta and gamma position to the oxygen attached to the phosphorus; or

together V and W are connected via an additional three carbon atoms to form an optionally substituted cyclic group containing six carbon atoms and is optionally substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy groups, wherein such substituent is attached to one of said carbon atoms that is three atoms away from an oxygen attached to the phosphorus atom; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

Z is selected from $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2(\text{aryl})$, $-\text{CH}(\text{aryl})\text{OH}$,

$-\text{CH}(\text{CH}=\text{CR}^2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2$, $-\text{OC}(\text{O})\text{R}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SC}(\text{O})\text{R}^3$,
 $-\text{SCO}_2\text{R}^3$, $-\text{NHC}(\text{O})\text{R}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NH}(\text{aryl})$, $-(\text{CH}_2)_p\text{OR}^{12}$, and $-(\text{CH}_2)_p\text{SR}^{12}$;

R^2 is selected from the group consisting of R^3 and hydrogen;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of hydrogen, and lower acyl; and

p is an interger 2 or 3;

with the provisos that:

a) V , Z , W , and W' are not all hydrogen; and

b) when Z is $-\text{R}^2$, then at least one of V , W , and W' is not hydrogen, alkyl, aralkyl, or alicyclic; and

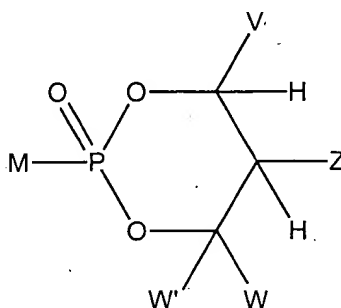
M is selected from the group that, attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$, is biologically active *in vivo* and that is attached to the phosphorus atom in Formula I via a carbon atom, with the proviso that MPO_3^{2-} is not an FBPase inhibitor;

wherein said compound of Formula I is converted to MPO_3H_2 by human liver microsomes;

pharmaceutically acceptable prodrugs and salts of Formula I;

and a pharmaceutically acceptable excipient.

15. (New) A pharmaceutical composition comprising a compound of Formula I:



Formula I

wherein:

V , W and W' are independently selected from the group consisting of hydrogen, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, wherein the cyclic group optionally contains one heteroatom and is substituted with a hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy group attached to a carbon atom that is three atoms away from both oxygen atoms that are attached to the phosphorus atom; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group wherein the cyclic group optionally contains one heteroatom, and is fused to an aryl group, at the beta and gamma position to the oxygen attached to the phosphorus; or

together V and W are connected via an additional three carbon atoms to form an optionally substituted cyclic group containing six carbon atoms and is optionally substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy groups, wherein such substituent is attached to one of said carbon atoms that is three atoms away from an oxygen attached to the phosphorus atom; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

Z is selected from $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2(\text{aryl})$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OC}(\text{O})\text{R}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SC}(\text{O})\text{R}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHC}(\text{O})\text{R}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NH}(\text{aryl})$, $-(\text{CH}_2)_p\text{OR}^{12}$, and $-(\text{CH}_2)_p\text{SR}^{12}$;

R^2 is selected from the group consisting of R^3 and hydrogen;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of hydrogen, and lower acyl; and

p is an interger 2 or 3;

with the provisos that:

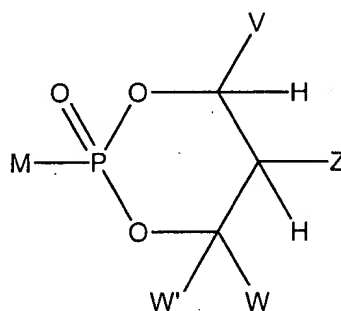
a) V, Z, W, and W' are not all hydrogen; and

b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not hydrogen, alkyl, aralkyl, or alicyclic; and

M is selected from the group that, attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$, is biologically active *in vivo* and that is attached to the phosphorus atom in Formula I via an oxygen atom, with the proviso that MPO_3^{2-} is not an FBPase inhibitor;

wherein said compound of Formula I is converted to MPO_3H_2 by human liver microsomes;
pharmaceutically acceptable prodrugs and salts of Formula I;
and a pharmaceutically acceptable excipient.

16. (New) A pharmaceutical composition comprising a compound of Formula I:



Formula I

wherein:

V, W and W' are independently selected from the group consisting of hydrogen, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, wherein the cyclic group optionally contains one heteroatom and is substituted with a hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy group attached to a carbon atom that is three atoms away from both oxygen atoms that are attached to the phosphorus atom; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group wherein the cyclic group optionally contains one heteroatom, and is fused to an aryl group, at the beta and gamma position to the oxygen attached to the phosphorus; or

together V and W are connected via an additional three carbon atoms to form an optionally substituted cyclic group containing six carbon atoms and is optionally substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and

aryloxycarbonyloxy groups, wherein such substituent is attached to one of said carbon atoms that is three atoms away from an oxygen attached to the phosphorus atom; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

Z is selected from $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2(\text{aryl})$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OC}(\text{O})\text{R}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SC}(\text{O})\text{R}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHC}(\text{O})\text{R}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NH}(\text{aryl})$, $-(\text{CH}_2)_p\text{OR}^{12}$, and $-(\text{CH}_2)_p\text{SR}^{12}$;

R^2 is selected from the group consisting of R^3 and hydrogen;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of hydrogen, and lower acyl; and

p is an interger 2 or 3;

with the provisos that:

a) V, Z, W, and W' are not all hydrogen; and

b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not hydrogen, alkyl, aralkyl, or alicyclic; and

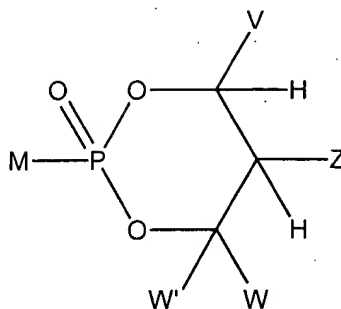
M is selected from the group that, attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$, is biologically active *in vivo* and that is attached to the phosphorus atom in Formula I via a nitrogen atom, with the proviso that MPO_3^{2-} is not an FBPase inhibitor;

wherein said compound of Formula I is converted to MPO_3H_2 by human liver microsomes;

pharmaceutically acceptable prodrugs and salts of Formula I;

and a pharmaceutically acceptable excipient.

17. (New) A pharmaceutical composition comprising a compound of Formula I:



Formula I

wherein:

W and W' are independently selected from the group of H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkynyl and 1-alkenyl;

Z is selected from $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2(\text{aryl})$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OC}(\text{O})\text{R}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SC}(\text{O})\text{R}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHC}(\text{O})\text{R}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NH}(\text{aryl})$, $-(\text{CH}_2)_p\text{OR}^{12}$, and $-(\text{CH}_2)_p\text{SR}^{12}$; or

together V and Z are connected via 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the oxygen attached to the phosphorus;

p is an integer 2 or 3;

R^2 is selected from the group of R^3 and $-\text{H}$;

R^3 is selected from the group of alkyl, aryl, alicyclic, and aralkyl;

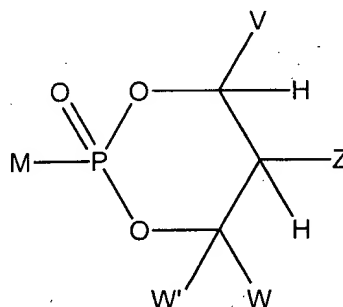
R^{12} is selected from the group consisting of hydrogen, and lower acyl; and

wherein said compound of formula I is converted to MPO_3H_2 by human liver microsomes, with the proviso that MPO_3^{2-} is not an FBPase inhibitor;

pharmaceutically acceptable prodrugs and salts of Formula I;

and a pharmaceutically acceptable excipient.

18. (New) A pharmaceutical composition comprising a compound of Formula I:



Formula I

wherein:

V, W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z is selected from the group of: $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{SR}^2$, $-\text{CH}_2\text{NHaryl}$, $-\text{CH}_2\text{aryl}$; or

together V and Z are connected via 3-5 carbon atoms to form a cyclic group, optionally containing heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from an oxygen attached to phosphorus;

R^2 is selected from the group of R^3 and H;

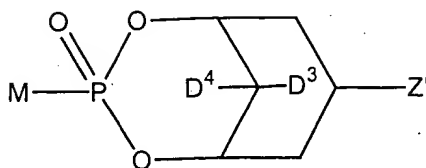
R^3 is selected from the group of alkyl, aryl, alicyclic, and aralkyl;

wherein said compound of formula I is converted to MPO_3H_2 by human liver microsomes, with the proviso that MPO_3^{2-} is not an FBPase inhibitor;

pharmaceutically acceptable prodrugs and salts of Formula I;

and a pharmaceutically acceptable excipient.

19. (New) A pharmaceutical composition comprising a compound of Formula VIII:



wherein:

Z' is selected from the group of $-OH$, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D^4 and D^3 are independently selected from the group of $-H$, alkyl, $-OR^2$, $-OH$, and $-OC(O)R^3$;
with the proviso that at least one of D^4 and D^3 are $-H$;

R^2 is selected from the group of R^3 and H ;

R^3 is selected from the group of alkyl, aryl, alicyclic, and aralkyl;

wherein said compound of formula I is converted to MPO_3H_2 by human liver microsomes, with
the proviso that MPO_3^{2-} is not an FBPase inhibitor;

and pharmaceutically acceptable prodrugs and salts of Formula VIII;

and a pharmaceutically acceptable excipient.--

REMARKS

Claims 2-13 are pending. Upon the entry of this amendment, claims 2-19 will be pending.

Support for these new claims can be found throughout the specification, for instance at pp. 49-51 and p.
56.

Respectfully Submitted,

Date: 3/27/02

By: Jessica R. Wolff
Jessica R. Wolff
Reg. No. 37,261

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